DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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CEPHEID
PAMELA JOHNSON
EXECUTIVE DIRECTOR, CLINICAL AFFAIRS
904 CARIBBEAN DRIVE
SUNNYVALE CA 94089-1189

February 19. 2015

Re: K143302
Trade/Device Name: Xpert® MTB/RIF
Regulation Number: 21 CFR 866.3373
Regulation Name: Nucleic acid-based *in vitro* diagnostic devices for the detection of *Mycobacterium tuberculosis* complex and the genetic mutations associated with *Mycobacterium tuberculosis* complex antibiotic resistance in respiratory specimens
Regulatory Class: Class II
Product Code: PEU
Dated: November 13, 2014
Received: November 19, 2014

Dear Ms. Johnson:

This letter corrects our substantially equivalent letter of February 12, 2015.

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Uwe Scherf -S for

Sally A. Hojvat, M. Sc., Ph.D.
Director
Division of Microbiology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*

K143302

Device Name

Xpert® MTB/RIF

Indications for Use *(Describe)*

The Xpert® MTB/RIF Assay, performed on the GeneXpert® Instrument Systems, is a qualitative, nested real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for the detection of *Mycobacterium tuberculosis* complex DNA in raw sputum or concentrated sputum sediment prepared from induced or expectorated sputum. In specimens where *Mycobacterium tuberculosis* complex (MTB-complex) is detected, the Xpert MTB/RIF Assay also detects the rifampin-resistance associated mutations of the *rpoB* gene.

The Xpert MTB/RIF Assay is intended for use with specimens from patients for whom there is clinical suspicion of tuberculosis (TB) and who have received no antituberculosis therapy, or less than three days of therapy. This test is intended as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings.

An Xpert MTB/RIF Assay result of "MTB NOT DETECTED" from either one or two sputum specimens is highly predictive of the absence of *M. tuberculosis* complex bacilli on serial fluorescent acid-fast sputum smears from patients with suspected active pulmonary tuberculosis and can be used as an aid in the decision of whether continued airborne infection isolation (AII) is warranted in patients with suspected pulmonary tuberculosis. The determination of whether testing of either one or two sputum specimens is appropriate for decisions regarding removal from AII should be based on specific clinical circumstances and institutional guidelines. Clinical decisions regarding the need for continued AII should always occur in conjunction with other clinical and laboratory evaluations and Xpert MTB/RIF Assay results should not be the sole basis for infection control practices.

The Xpert MTB/RIF Assay must always be used in conjunction with mycobacterial culture to address the risk of false negative results and to recover organisms when MTB-complex is present for further characterization and drug susceptibility testing. However, decisions regarding the removal of patients from AII need not wait for culture results. Sputum specimens for TB culture, AFB smear microscopy, and Xpert MTB/RIF Assay testing should follow CDC recommendations with regard to collection methods and time frame between specimen collection.

The Xpert MTB/RIF Assay does not provide confirmation of rifampin susceptibility since mechanisms of rifampin resistance other than those detected by this device may exist that may be associated with a lack of clinical response to treatment.

Specimens that have both MTB-complex DNA and rifampin-resistance associated mutations of the *rpoB* gene detected by the Xpert MTB/RIF Assay must have results confirmed by a reference laboratory. If the presence of rifampin-resistance associated mutations of the *rpoB* gene is confirmed, specimens should also be tested for the presence of genetic mutations associated with resistance to other drugs.

The Xpert MTB/RIF Assay should only be performed in laboratories that follow safety practices in accordance with the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories publication and applicable state or local regulations.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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5.0 510(k) Summary

As required by 21 CFR Section 807.92(c).

Submitted by:	Cepheid® 904 Caribbean Drive Sunnyvale, CA 90489 Phone number: (408) 400-8460 Fax number: (847) 510-0539 E-mail: kerry.flom@cepheid.com
Contact:	Kerry J. Flom, Ph.D.
Date of Preparation:	November 13, 2014
Device:	
Trade name:	Xpert® MTB/RIF
Common name:	Xpert MTB/RIF Assay
Type of Test:	Qualitative, nested real-time polymerase chain reaction (PCR)
Regulation number/ Classification name/ Product code:	866.3373/ System, nucleic acid-based, mycobacterium tuberculosis complex, resistance marker, direct specimen/ PEU
Classification Advisory Panel	Microbiology (83)
Predicate Devices Name(s):	Xpert MTB/RIF

Device Description:

The Xpert MTB/RIF Assay is a qualitative, automated, *in vitro* diagnostic test for qualitative detection of *Mycobacterium tuberculosis* (MTB) complex DNA in raw sputum samples or in concentrated sputum sediments prepared from induced or expectorated sputa that are either acid-fast bacilli (AFB) smear positive or negative. The assay is performed on the Cepheid GeneXpert Instrument Systems. The Xpert MTB/RIF Assay on the GeneXpert Instrument System automates and integrates sample preparation, nucleic acid amplification, and detection of the target sequences in simple or complex samples using real-time PCR. The system consists of an instrument, personal computer, and preloaded software for running the tests and viewing the results. The system requires the use of single-use disposable cartridges that hold the PCR reagents and host the PCR process. Because the cartridges are self-contained, cross-contamination between samples is minimized.

The Xpert MTB/RIF Assay includes reagents for the detection of MTB and Rifampin (RIF) resistance from raw sputum samples and in prepared sputum sediments. A Sample

Processing Control (SPC) and a Probe Check Control (PCC) are also included in the cartridge. The SPC is present to control for adequate processing of the target bacteria and to monitor for the presence of inhibitors in the PCR reaction. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

The GeneXpert Instrument Systems, comprised of the GeneXpert Dx Systems, the GeneXpert Infinity-48 System, the GeneXpert Infinity-48s, and the GeneXpert Infinity-80 System, have 1 to 80 randomly accessible modules, depending upon the instrument, that are each capable of performing separate sample preparation and real-time PCR tests. Each module contains a syringe drive for dispensing fluids (i.e., the syringe drive activates the plunger that works in concert with the rotary valve in the cartridge to move fluids between chambers), an ultrasonic horn for lysing cells or spores, and a proprietary I-CORE® thermocycler for performing real-time PCR and detection.

Device Intended Use:

The Xpert® MTB/RIF Assay, performed on the GeneXpert® Instrument Systems, is a qualitative, nested real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for the detection of *Mycobacterium tuberculosis* complex DNA in raw sputum or concentrated sputum sediment prepared from induced or expectorated sputum. In specimens where *Mycobacterium tuberculosis* complex (MTB-complex) is detected, the Xpert MTB/RIF Assay also detects the rifampin-resistance associated mutations of the *rpoB* gene.

The Xpert MTB/RIF Assay is intended for use with specimens from patients for whom there is clinical suspicion of tuberculosis (TB) and who have received no antituberculosis therapy, or less than three days of therapy. This test is intended as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings.

An Xpert MTB/RIF Assay result of "MTB NOT DETECTED" from either one or two sputum specimens is highly predictive of the absence of *M. tuberculosis* complex bacilli on serial fluorescent acid-fast sputum smears from patients with suspected active pulmonary tuberculosis and can be used as an aid in the decision of whether continued airborne infection isolation (AII) is warranted in patients with suspected pulmonary tuberculosis. The determination of whether testing of either one or two sputum specimens is appropriate for decisions regarding removal from AII should be based on specific clinical circumstances and institutional guidelines. Clinical decisions regarding the need for continued AII should always occur in conjunction with other clinical and laboratory evaluations and Xpert MTB/RIF Assay results should not be the sole basis for infection control practices.

The Xpert MTB/RIF Assay must always be used in conjunction with mycobacterial culture to address the risk of false negative results and to recover organisms when MTB-complex is present for further characterization and drug susceptibility testing. However, decisions regarding the removal of patients from AII need not wait for culture

results. Sputum specimens for TB culture, AFB smear microscopy, and Xpert MTB/RIF Assay testing should follow CDC recommendations with regard to collection methods and time frame between specimen collection.

The Xpert MTB/RIF Assay does not provide confirmation of rifampin susceptibility since mechanisms of rifampin resistance other than those detected by this device may exist that may be associated with a lack of clinical response to treatment.

Specimens that have both MTB-complex DNA and rifampin-resistance associated mutations of the *rpoB* gene detected by the Xpert MTB/RIF Assay must have results confirmed by a reference laboratory. If the presence of rifampin-resistance associated mutations of the *rpoB* gene is confirmed, specimens should also be tested for the presence of genetic mutations associated with resistance to other drugs.

The Xpert MTB/RIF Assay should only be performed in laboratories that follow safety practices in accordance with the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories publication and applicable state or local regulations.

Substantial Equivalence:

Predicate device name(s): Cepheid Xpert® MTB/RIF Assay

Predicate 510(k) number(s): K131706

Comparison with predicate:

The Xpert MTB/RIF Assay is substantially equivalent to the current Xpert MTB/RIF Assay [510(k) #K131706].

Similarities and differences between the Cepheid Xpert MTB/RIF Assay and the predicate device are shown in Table 5.1.

A prospective multi-center study (Study 2) was conducted at multiple sites in the United States, as well as South Africa and Brazil. Performance of the MTB/RIF Assay was assessed as an alternative to fluorescent stained AFB-smear microscopy as an aid in determining the need for continued airborne infection isolation in patients with suspected active pulmonary tuberculosis. The clinical data demonstrated that a single negative Xpert MTB/RIF result predicted the absence of AFB smear-positive pulmonary tuberculosis with an overall negative predictive value (NPV) of 99.7% (99.6% in the U.S. and 100% in non-U.S.). Two serial negative Xpert MTB/RIF Assay results predicted the absence of AFB smear-positive pulmonary tuberculosis with an overall NPV of 100%.

Table 5.1. Comparison of Similarities and Differences of the proposed Xpert MTB/RIF Assay with the Predicate Device

	Device	Predicate
Item	**Cepheid Xpert MTB/RIF**	**Current Cepheid Xpert MTB/RIF**
510(k) Number	To be assigned	#K131706
Regulation	Same	866.3373
Product Code	Same	PEU
Device Class	Same	II
Technology/ Detection	Same	Multiplex real time RT/PCR
Indication for Use	Same	Patients for whom there is clinical suspicion of tuberculosis (TB) and who have received no antituberculosis therapy, or less than 3 days of therapy
Assay Targets	Same	MTB-complex DNA and Rif resistance associated mutations
Specimen Types	Same	Raw sputum samples or concentrated sputum sediments
Technological Principles	Same	Real-time PCR
Nucleic Acid Extraction	Same	Yes
Extraction Methods	Same	Sample preparation integrated in GeneXpert Cartridge and GeneXpert Instrumentation System
Assay Results	Same	Qualitative
Instrument System	Same	Cepheid GeneXpert Instrument Systems
Assay Controls	Same	Sample Processing Control (SPC) and Probe Check Control (PCC). Failures result in single sample repeat.
Rapid test results	Same	Total 120 minutes for sample preparation and real-time PCR
Laboratory Users	Same	CLIA Moderate or High Complexity

Differences		
	Device	**Predicate**
Item	**Cepheid Xpert MTB/RIF**	**Current Cepheid Xpert MTB/RIF**
Intended Use	The Xpert® MTB/RIF Assay, performed on the GeneXpert® Instrument Systems, is a qualitative, nested real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for the detection of *Mycobacterium tuberculosis* complex DNA in raw sputum or concentrated sputum sediment prepared from induced or expectorated sputum. In specimens where *Mycobacterium tuberculosis* complex (MTB-complex) is detected, the Xpert MTB/RIF Assay also detects the rifampin-resistance associated mutations of the *rpoB* gene. The Xpert MTB/RIF Assay is intended for use with specimens from patients for whom there is clinical suspicion of tuberculosis (TB) and who have received no antituberculosis therapy, or less than three days of therapy. This test is intended as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings. An Xpert MTB/RIF Assay result of "MTB NOT DETECTED" from either one or two sputum specimens is highly predictive of the absence of *M. tuberculosis* complex bacilli on serial fluorescent acid-fast sputum smears from patients with suspected active pulmonary tuberculosis and can be used as an aid in the decision of whether continued airborne infection isolation (AII) is warranted in patients with suspected pulmonary tuberculosis. The determination of whether testing of either one or two sputum specimens is appropriate for decisions regarding	The Xpert® MTB/RIF Assay, performed on the GeneXpert® Instrument Systems, is a qualitative, nested real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for the detection of *Mycobacterium tuberculosis* complex DNA in raw sputum or concentrated sediments prepared from induced or expectorated sputum. In specimens where *Mycobacterium tuberculosis* complex (MTB-complex) is detected, the Xpert MTB/RIF Assay also detects the rifampin-resistance associated mutations of the *rpoB* gene. The Xpert MTB/RIF Assay is intended for use with specimens from patients for whom there is clinical suspicion of tuberculosis (TB) and who have received no antituberculosis therapy, or less than 3 days of therapy. This test is intended as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings. The Xpert MTB/RIF Assay does not provide confirmation of rifampin susceptibility since mechanisms of rifampin resistance other than those detected by this device may exist that may be associated with a lack of clinical response to treatment. Specimens that have both MTB-complex DNA and rifampin-resistance associated mutations of the *rpoB* gene detected by the Xpert MTB/RIF Assay must have results confirmed by a reference laboratory. If the presence of rifampin-resistance associated mutations of the *rpoB* gene is confirmed, specimens should also be tested for the presence of genetic mutations associated with resistance to other drugs.

Differences		
	Device	**Predicate**
Item	**Cepheid Xpert MTB/RIF**	**Current Cepheid Xpert MTB/RIF**
	removal from AII should be based on specific clinical circumstances and institutional guidelines. Clinical decisions regarding the need for continued AII should always occur in conjunction with other clinical and laboratory evaluations and Xpert MTB/RIF Assay results should not be the sole basis for infection control practices. The Xpert MTB/RIF Assay must always be used in conjunction with mycobacterial culture to address the risk of false negative results and to recover organisms when MTB-complex is present for further characterization and drug susceptibility testing. However, decisions regarding the removal of patients from AII need not wait for culture results. Sputum specimens for TB culture, AFB smear microscopy, and Xpert MTB/RIF Assay testing should follow CDC recommendations with regard to collection methods and time frame between specimen collection. The Xpert MTB/RIF Assay does not provide confirmation of rifampin susceptibility since mechanisms of rifampin resistance other than those detected by this device may exist that may be associated with a lack of clinical response to treatment. Specimens that have both MTB-complex DNA and rifampin-resistance associated mutations of the *rpoB* gene detected by the Xpert MTB/RIF Assay must have results confirmed by a	The Xpert MTB/RIF Assay must be used in conjunction with mycobacterial culture to address the risk of false negative results and to recover the organisms for further characterization and drug susceptibility testing. The Xpert MTB/RIF Assay should only be performed in laboratories that follow safety practices in accordance with the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories publication and applicable state or local regulations.

Differences		
	Device	**Predicate**
Item	**Cepheid Xpert MTB/RIF**	**Current Cepheid Xpert MTB/RIF**
	reference laboratory. If the presence of rifampin-resistance associated mutations of the *rpoB* gene is confirmed, specimens should also be tested for the presence of genetic mutations associated with resistance to other drugs. The Xpert MTB/RIF Assay should only be performed in laboratories that follow safety practices in accordance with the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories publication and applicable state or local regulations.	

Non-Clinical Studies:

Analytical Sensitivity

Please refer to the previously FDA-cleared 510(k) #K131706.

Analytical Reactivity (Inclusivity)

Please refer to the previously FDA-cleared 510(k) #K131706.

Analytical Specificity (Exclusivity)

Potential cross-reactivity of eight microorganisms was evaluated by *in silico* analysis. All eight microorganisms tested revealed no potential for cross-reactivity. See Table 5.2 below.

Table 5.2. Microorganisms Predicted to be Non-Cross Reactive by *In Silico* Analysis

Mycobacterium chimaera	*Mycobacterium immunogenum*
Mycobacterium avium subsp. paratuberculosis	*Mycobacterium massiliense*
Mycobacterium avium subsp. silvaticum	*Mycobacterium bolletii*
Mycobacterium avium subsp. hominissuis	
Mycobacterium franklinii	

Please refer to the previously FDA-cleared 510(k) #K131706 for a description of additional analytical specificity testing performed.

Interfering Substances

Please refer to the previously FDA-cleared 510(k) #K131706.

Carry-Over Contamination Study

Please refer to the previously FDA-cleared 510(k) #K131706.

RIF Resistance Study

Please refer to the previously FDA-cleared 510(k) #K131706.

Linearity

Not applicable, the Xpert MTB/RIF Assay is a qualitative assay.

Clinical Performance Characteristics:

Reproducibility

Please refer to the previously FDA-cleared 510(k) #K131706.

Instrument System Precision

Please refer to the previously FDA-cleared 510(k) #K131706.

Clinical Performance Study

Xpert MTB/RIF Assay Performance in an HIV Population

To compare performance of the Xpert MTB/RIF Assay in HIV-infected and HIV-uninfected subjects, data from Study 2 were analyzed by smear status of specimens and HIV status of the population. Tables 5.3 and 5.4 compare the sensitivities and specificities of one Xpert MTB/RIF Assay result in specimens obtained from HIV-infected and HIV-uninfected subjects stratified by AFB smear-positive and AFB smear-negative results, respectively. For both HIV-infected and HIV-uninfected subjects, the sensitivity of the Xpert MTB/RIF Assay for detection of MTB-complex was higher in AFB smear-positive specimens (100.0% and 97.8%, respectively) than in AFB smear-negative specimens (52.1% and 58.3%, respectively). These data are summarized in Table 5.4.

Table 5.3. Comparison of Sensitivity and Specificity of One Xpert MTB/RIF Assay Result in HIV-Infected and HIV-Uninfected Subjects – AFB Smear Positive Only

Xpert MTB/RIF	Overall	HIV-infected	HIV-uninfected	Difference (95% CI)
Sensitivity	98.5% (129/131)	100% (39/39)	97.8% (90/92)	2.2% (-0.8%, 5.2%)
Specificity	94.4% (17/18)	100% (7/7)	90.9% (10/11)	9.1% (-7.9%, 26.1%

Table 5.4. Comparison of Sensitivity and Specificity of One Xpert MTB/RIF Assay Result in HIV-Infected and HIV-Uninfected Subjects – AFB Smear Negative Only

Xpert MTB/RIF	Overall	HIV-infected	HIV-uninfected	Difference (95% CI)
Sensitivity	54.8% (46/84)	52.1% (25/48)	58.3% (21/36)	-6.3% (-27.7%, 15.2%)
Specificity	98.8% (718/721)	98.2% (332/338)	99.2% (386/389)	-1.0% (-2.7%, 0.7%)

Xpert MTB/RIF Assay Performance as Basis for Removal of Patients from Respiratory Isolation

Tables 5.5 and 5.6 present the overall performance of one Xpert MTB/RIF Assay result compared to the results of MTB culture, stratified by AFB smear result (Table 5.5). Table 5.6 is a side-by-side comparison of the performance of one Xpert MTB/RIF Assay result versus the composite result of two AFB smears in U.S. and non-U.S. subjects (N=960). Overall sensitivity of one Xpert MTB/RIF Assay in AFB smear-positive and AFB smear-negative subjects (based on two AFB smears) was 98.5% (95% CI: 94.6%,99.6%) and 54.8% (95% CI: 44.1%, 65.0%) respectively, and overall specificity was 98.7% (95% CI: 97.5%, 99.3%). One Xpert MTB/RIF Assay result of **MTB Not Detected** was associated with a probability of MTB culture-positive/AFB smear-positive results of 0.4% for U.S. subjects and 0.0% for non-U.S. subjects.

Table 5.5. Performance of One Xpert MTB/RIF Assay Result Stratified by Two AFB Smears Relative to MTB Culture in U.S. and non-U.S. Subjects

		Culture						
		Positive			Negative			Total
		AFB Smear +	AFB Smear -	Overall Culture +	AFB Smear +	AFB Smear -	Overall Culture -	
Xpert MTB/RIF Assay	Positive	129	46	175	1	9	10[a]	185
	Negative	2	38	40	17	718	735	775
	Total	131	84	215	18[b]	727	745	960

Performance of Xpert MTB/RIF Assay for Smear Positive:
Sensitivity: 98.5% (129/131), 95% CI: 94.6%,99.6%
Specificity: 94.4% (17/18), 95% CI: 74.2%, 99.0%

Performance of Xpert MTB/RIF Assay for Smear Negative:
Sensitivity: 54.8% (46/84), 95% CI: 44.1%, 65.0%
Specificity: 98.8% (718/727), 95% CI: 97.7%, 99.4%

Prevalence of MTB Culture Positive: 22.4% (215/960)
Prevalence of MTB Culture Positive in U.S. subjects: 14.2% (88/618)
Prevalence of MTB Culture positive in non-U.S. subjects: 37.1% (127/342)

Percent of AFB smear positive subjects among subjects with MTB Culture Positive: 60.9% (131/215)

Overall Probability of MTB Culture Positive among subjects with an Xpert MTB/RIF Negative Result: 5.2% (40/775), 95% CI: 3.8%, 7.0%
Probability of MTB Culture Positive among subjects with an Xpert MTB/RIF Negative Result (U.S. subjects): 2.4% (13/539), 95% CI: 1.4%, 4.1%

Probability of MTB Culture Positive among subjects with an Xpert MTB/RIF Negative Result (non-U.S. subjects): 11.4% (27/236), 95% CI: 8.0%, 16.1%

Overall Probability of MTB Culture Positive and AFB smear positive among subjects with an Xpert MTB/RIF Negative Result: 0.3% (2/775), 95% CI: <0.1%, 0.9%

Probability of MTB Culture Positive and AFB smear positive among subjects with an Xpert MTB/RIF Negative Result (U.S. subjects): 0.4% (2/539), 95% CI: 0.1%, 1.3%

Probability of MTB Culture Positive and AFB smear positive among subjects with an Xpert MTB/RIF Negative Result (non-U.S.) subjects: 0.0% (0/236), 95% CI: 0.0%, 1.6%

[a]Of the 10 MTB culture-negative specimens that were positive by Xpert MTB/RIF Assay, 5 grew non-tuberculosis mycobacteria (NTM). MTB-complex was isolated and identified using standard of care methods not associated with the study protocol in 4 of the 5 specimens.
[b]Of the 18 MTB culture-negative/AFB smear-positive specimens, 14 grew NTM.

One Xpert MTB/RIF Assay was associated with a sensitivity of 81.4% (95% CI: 75.7%, 86.0%) for identifying MTB culture-positive subjects compared to a sensitivity of 60.9% (95% CI: 54.3%, 67.2%) for two AFB smears.

Table 5.6. Comparison Of Performance of One Xpert MTB/RIF Assay Result vs Two AFB Smears Each Versus MTB Culture in U.S. and non-U.S. Subjects

One Xpert MTB/RIF Assay Results		Culture		
		Positive	Negative	Total
Xpert	Positive	175	10	185
	Negative	40	735	775
	Total	215	745	960
Sensitivity:		81.4% (95% CI: 75.7, 86.0)		
Specificity:		98.7% (95% CI: 97.5, 99.3)		
U.S. prevalence		14.2% (95% CI: 11.7, 17.2)		
PPV:		94.9% (95% CI: 87.7, 98.0)		
NPV:		97.6% (95% CI: 95.9, 98.6)		
Non-U.S. prevalence		37.1% (95% CI: 32.2, 42.4)		
PPV		94.3% (95% CI: 88.2, 97.4)		
NPV		88.6 (95% CI: 83.9, 92.0)		

Two AFB Smears		Culture		
		Positive	Negative	Total
AFB Smear	Positive	131	18	149
	Negative	84	727	811
	Total	215	745	960
Sensitivity:		60.9% (95% CI: 54.1, 67.5)		
Specificity:		97.6% (95% CI: 96.2, 98.6)		
U.S. prevalence		14.2% (95% CI: 11.7, 17.2)		
PPV:		77.2% (95% CI: 66.8, 85.1)		
NPV:		95.0% (95% CI: 92.8, 96.5)		
Non-U.S. Prevalence:		37.1% (95% CI: 32.2, 42.4)		
PPV		100% (95% CI: 94.8, 100)		
NPV		79.0% (95% CI: 73.8, 83.5)		

In U.S. subjects, the NPV for one Xpert MTB/RIF Assay result was 97.6% (95% CI: 95.9%, 98.6%) while the NPV for two AFB smears results was 95.0% (95% CI: 92.8%, 96.5%) with a prevalence of TB in U.S. subjects of 14.2%. The difference in NPVs was 2.6% with 95% CI: 1.2%, 4.2%.

Proposed Labeling

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

Conclusions

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.